

Enuresis Persisting into Adulthood

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Introduction: Nocturnal enuresis is a very common finding in children to the extent that many families and caregivers, alike, may dismiss it as a developmental stage rather than a disease. Persistence of nocturnal enuresis into adulthood, however, has received little discussion and is surrounded by fallacies.

Materials and Methods: All existing literature cited in PubMed between 1970 and 2005 were reviewed using the search entries “nocturnal enuresis AND adult*”.

Result: Of the 220 papers reviewed, enuresis persisting into adulthood was covered in only 87. Those aspects pertinent to this subset of patients were placed in focus.

Conclusion: In contrast to the numerous researches on childhood enuresis, persistent adulthood enuresis is an underdiscussed subject, distinct in a few aspects of its etiology and management described herein.

Keywords: enuresis, adult, nocturia

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INTRODUCTION

Nocturnal enuresis (NE) is a very common finding in children, to the extent that many families and caregivers, alike, may dismiss it as a developmental stage rather than a disease. Currently, an estimated 5 to 7 million children in the United States have primary NE. A similar rate has been reported in other countries.⁽¹⁾ Despite the spontaneous resolution rate of 15% per year, enuresis persists in 1.5% to 3% of the adult population.⁽²⁾

This article reviews current information on primary NE persisting into adulthood, describes various aspects of its etiology and management, and provides an updated and comprehensive review of this disorder.

DEFINITION

According to the International

Children's Continence Society (ICCS), urinary incontinence denotes involuntary loss of urine that happens both day and night or in either portion.⁽³⁾ Nocturnal enuresis or common enuresis is defined as involuntary loss of urine that occurs only at night, specifically during sleep. Based on the presence of a period of dryness, nocturnal enuresis is categorized as primary—a child who has never had a dry period for at least 6 months; and secondary—a child who has experienced at least 6 months of nighttime dryness.

The criterion for the period required to meet this definition varies in the literature between 6 months and 1 year. Based on the Diagnostic and Statistical Manual of Mental Disorders—fourth edition (DSM-IV), a primary nocturnal enuretic patient is defined as an individual who has never established urinary continence, and secondary nocturnal enuresis is

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Table 1. Classification Schemes for Enuresis

Basis of Classification	Classes
Time of enuresis	Nocturnal enuresis: passing urine while asleep Diurnal enuresis or incontinence: leakage of urine during the day
Other symptoms	Monosymptomatic or uncomplicated nocturnal enuresis: normal voiding occurring at night in bed in the absence of other symptoms referable to the urogenital or gastrointestinal tract Polysymptomatic or complicated nocturnal enuresis: bed-wetting associated with daytime symptoms such as urgency, frequency, chronic constipation, or encopresis
Previous periods of dryness	Primary enuresis: bed-wetting in a child who has never been dry Secondary enuresis: bed-wetting in a child who has had at least six months of nighttime dryness

defined as a disturbance developed after a period of established urinary continence. In this paper, primary NE is defined as bed-wetting since birth. Table 1 lists typical classification schemes for enuresis.

EPIDEMIOLOGY

The prevalence of primary nocturnal enuresis (PNE) in adults varies from 0.19% to 3.8% in different studies.⁽⁴⁻⁹⁾ It is suggested that bias in reporting might have played a role in epidemiological surveys on the adolescent and adult population, for such patients may be reluctant to report that they suffer from NE.

In 1943, Levine⁽⁴⁾ first reported that 1.2% of the army recruits were still bed-wetters at 18. Between 1944 and 1954, additional prevalence studies were conducted on the recruits and estimated the prevalence of PNE from 0.19% to 2.5%.⁽⁵⁻⁸⁾ These variations result from applying different definitions for NE by the investigators. In addition, they have not included women in their studies; thus, it is of limited value to generalize the results beyond their study population.

To clarify these issues, Cushing and Baller⁽⁹⁾ performed a prevalence study among graduates and undergraduates. Of 398 students participating in this study, 3.8% had PNE. Moreover, two prospective cohort studies were initiated focusing on NE persisting into adulthood. One Swedish cohort study⁽¹⁰⁾ was based on a questionnaire mailed to 1034 teenagers in 1995 who had previously been evaluated at age 7. The prevalence of PNE was 0.7% in men and 0.6% in women at 17 years of age among the 736 respondents. The second cohort study was designed to determine the prevalence and natural history of incontinence among healthy adolescent school children.⁽¹¹⁾ Beginning in 1994, urinary symptoms were obtained from 1176 school children at ages 11

to 12 years and again at 15 to 16 years. Nocturnal enuresis was reported by 4.7% of children at 11 to 12 (3.5% in girls and 6.25% in boys) and 1.1% at 15 to 16 years old (0.8% and 1.6%, respectively). Nocturnal enuresis was more frequent among boys in both age groups and day-wetting was more frequent in girls.

More recently, two large population-based cross-sectional studies have been performed to identify the characteristics of the PNE in adults. In the Netherlands, 13081 non-institutionalized adults (18 to 64 years old) were asked to participate in a study in January through March 1996.⁽¹²⁾ Of those approached, 11406 (87%) agreed to complete a personal questionnaire. The definition was based on bed-wetting once a month or more. Their overall prevalence of NE was 0.5%. Half of the enuretic men and 19% of the women had PNE. There was no significant difference in the prevalence of NE between the age groups and sexes.

The second study was a survey in Hong Kong.⁽¹³⁾ In this study, 13086 people were contacted randomly and data were obtained by telephone interview. The response rate was 65%. The overall prevalence of PNE was 2.35% (2.7% in men and 2% in women). Fifty percent of the patients wetted their bed more than 3 nights per week and 26% every night. In addition, 18.4% of the enuretics also complained of daytime incontinence. In both reports, there was no significant difference in the prevalence of PNE between the age groups. The authors concluded that in adults, NE showed no trend to spontaneous improvement as age increases. In addition, finding a high prevalence of severe NE, they suggested that PNE persisting into adulthood represents a more pronounced and refractory form of the condition. The studies on the prevalence of PNE in adults are summarized in Table 2.

Table 2. Studies on Prevalence of Primary Nocturnal Enuresis*

Authors	Year of Publication	Patients' Age, y	Prevalence
Levine ⁽⁴⁾	1943	18	1.2%
Wadsworth ⁽⁵⁾	1944	NA	0.7% to 2.0%
Turner and Taylor ⁽⁶⁾	1974	NA	0.7% to 2.0%
Thorne ⁽⁷⁾	1944	18	1.0% to 2.5%
Bieger ⁽⁸⁾	1954	NA	0.2%
Cushing and Baller ⁽⁹⁾	1975	NA	1.6% to 3.8%
Hellstrom and colleagues ⁽¹⁰⁾	1995	17	0.7%
Swithinbank and colleagues ⁽¹¹⁾	1998	15 to 16	1.1%
Hirasing and colleagues ⁽¹²⁾	1997	18 to 64	0.5%
Yeung and colleagues ⁽¹³⁾	2004	16 to 40	2.3%

*NA indicates not available.

In summary, depending on whether data have been accumulated by direct interview or hand-in questionnaire, women have been included or not, etc, results on the prevalence of the adulthood enuresis have varied, ranging from 0.5% to 2.7%.

ETIOLOGY

From an etiologic standpoint, NE is a heterogeneous disorder and several pathophysiological mechanisms contribute to its initiation, severity, and degree of associated symptoms. Numerous etiologic factors have been investigated and various theories have been proposed. The most likely explanation for NE is a complicated interplay among the nocturnal urine production, the nocturnal functional bladder capacity, and the sleep patterns. All adults are at risk of NE if nocturnal diuresis exceeds the functional bladder capacity, provided that they are not awakened by imminent bladder contraction or the strong desire to void.

Evidence suggests that the PNE persisting into adulthood may differ from that of children in its underlying pathophysiological mechanisms. A higher incidence of severe forms of NE plus a very low rate of spontaneous cure support the notion of a more complex pathology in adults.

Genetics

Nocturnal enuresis is a complex disorder in which both genetic and environmental factors (somatic and psychosocial) play a role, although at proportionally different contributions. In addition to genetic/environmental interactions, enuresis appears to be under the influence of multiple genes.⁽¹⁴⁾

Enuresis has been suspected of having a genetic

component at least since 1935, when Frary found a higher incidence of enuresis in affected relatives than the general population.⁽¹⁵⁾ Frary's statement was confirmed by studies demonstrating an increased prevalence of enuresis among the first-degree relatives of the enuretic subjects.^(16,17) In one review, it was found that the risk for NE was 77% if both parents were affected. The risk declined to 43% when only one parent had a history of enuresis, and to 15% when neither parent was enuretic.⁽¹⁸⁾

In 1997, von Gontard and colleagues found a positive family history in 63.2% of patients, with 22.2% of fathers, 23.9% of the mothers, and 16.5% of the siblings being affected.⁽¹⁹⁾ In a cross-sectional epidemiological study, Yeung and colleagues evaluated characteristics of adults with PNE in Hong Kong and found a positive family history in 13.1% of subjects.⁽¹³⁾ Another study by Nappo and associates on 107 enuretic adolescents (mean age, 15.3 years; range, 13 to 23 years) identified up to 80% of adolescents with NE to have a positive family history of NE.⁽²⁰⁾ There was no difference in the prevalence of positive family history between primary and secondary enuretics, as in von Gontard's study.⁽¹⁹⁾

The exact mechanisms underlying this family aggregation are unknown. According to a study by Arnell and coworkers in 1997, about 45% of the NE cases are compatible with an autosomal dominant mode of inheritance.⁽²¹⁾ In 1995, Birch and Miller evaluated the bladder function over 3 generations in a family of which two members had undergone clam enterocystoplasty for refractory PNE.⁽²²⁾ Eight members had the history of PNE persisting into adolescence and 4 members (age range, 20 to 39 years) had PNE with urodynamically proved detrusor

instability. The authors concluded that detrusor instability had, at least in part, a genetic basis with autosomal dominant mode of transmission in family members with a history of current or past PNE. This finding was in agreement with previous studies that had suggested the most common mode to be an autosomal dominant transmission.⁽²³⁾

In summary, adulthood enuresis is a hereditary disease like its childhood counterpart, and it may follow an autosomal dominant genetic pattern with a strong environmental influence.

Bladder Physiology

Debate is ongoing about the role of abnormalities of bladder function in NE. The results of urodynamic studies suggest that NE is different in adults and children. However, the incidence of anatomical and functional bladder abnormalities in enuretic children is similar to that in the normal population.^(24,25)

In 1994, Robertson and colleagues assessed the bladder function in 17 healthy volunteers and detrusor instability was found in 17% on filling cystometry, filling at a rate of 50 mL/min.⁽²⁶⁾ Wyndaele reported an incidence of 11% among 38 volunteers with a negative urologic history, as well.⁽²⁷⁾ On the contrary, the incidence of urodynamic abnormalities on conventional assessment in adults with PNE lies between 28.8% and 93% in different studies, much higher than that in normal volunteers. In one filling cystometric analysis of 39 adults with enuresis, the rate of urodynamic abnormalities was found to be 28.2%, and the most common abnormality was detrusor instability.⁽²⁸⁾ In another study, Yeung and coworkers reported a greater rate of urodynamic abnormalities in the adults with PNE.⁽²⁹⁾ Again, detrusor overactivity was the most common finding in 93% of the patients, more often moderate to severe. The high rate of detrusor instability in this study was in part due to the evaluation of the selected patients with moderate or severe enuretic symptoms and mild cases were not included in this study. Of the 30 patients with moderate or severe PNE, 16 (53%) had also significantly reduced bladder capacity (less than 300 mL). In addition, 73% of patients had urodynamic evidence of functional bladder outflow obstruction including dysfunctional voiding and detrusor sphincter or detrusor pelvic discoordination. The authors concluded that PNE in adults is not

only a psychologically disturbing condition, but also a urological disorder with a significant underlying bladder dysfunction that warrants special attention. These results and the work of preceding investigators suggest that PNE in adults is a cause rather than the result of psychological disturbance. Detrusor instability has its impact on both filling properties of the bladder as well as symptoms.

Wadie reported the urodynamic evaluation of 52 enuretic adults.⁽³⁰⁾ Detrusor instability was recognized in 20 (38.5%) of those enrolled in the study. Interestingly, the author found a significant effect of detrusor instability on both bladder capacity and compliance. The average capacity value was approximately 140 mL lower in the patients with detrusor instability compared with the patients with a stable bladder. Similarly, in another urodynamic study performed by Yucel and associates, differences in the maximal bladder capacity and compliance between the patients with and without instability were statistically significant and all hypocompliant cases had detrusor instability.⁽³¹⁾ Interestingly, however, in both studies the overall cystometric capacity and compliance in patients with persistent PNE had fallen to the reference range for adults as depicted by Wyndaele.⁽²⁷⁾ In addition, voiding pressure had been normal in the patients.

Nighttime and daytime bladder capacities are not equal and reduction in the nighttime bladder capacity may be an important cause of NE.⁽³²⁾ A study on the overnight natural filling cystometries in 26 patients (age range, 8 to 36 years) with resistant PNE supported this statement.⁽³³⁾ Of 16 patients who were healthy on conventional urodynamic assessment, 10 showed involuntary detrusor contraction during the night.

In conclusion, urodynamic analysis of the bladder function and coordination in enuretic adults has been in stark contrast to children. In adults, we may expect a 38.5% instability on conventional urodynamics which can grow to 77% if sleep urodynamics are included.

Nocturnal Urine Production

A circadian rhythm of urine production is developed from early childhood with a marked nocturnal reduction in diuresis to about 50% of the daytime levels.⁽³⁴⁾ It has been postulated that normal

development may include the establishment of a circadian rhythm in release of the hormones that regulate free water or solute excretion.^(35,36) Such a normal circadian variation in urine production is absent in a significant proportion of the patients with monosymptomatic PNE (MPNE). These patients produce large quantities of dilute urine at nights which exceed the bladder capacity. Failure of such a child to wake up results in an enuretic episode.⁽³⁷⁾

In 1951, Mills first provided evidence of nocturnal polyuria in some children with NE and suggested that nocturnal urine production exceeding the bladder capacity might play a role in the pathophysiology of NE.⁽³⁸⁾ This finding led to many more studies in the following decades documenting nocturnal polyuria and its underlying causes. The circadian rhythm of various urine output modulating hormones has been investigated. Most hormone levels have proved to be normal except for arginine vasopressin (AVP).

Abnormal diurnal rhythm of AVP with lack of the normal nocturnal rise has been reported in children with NE,^(39,40) and seems to correlate with nocturnal polyuria as well as response to the AVP analogue (desmopressin).^(41,42) A subgroup of the patients with NE who respond to desmopressin generally has normal functional bladder capacity and increased nocturnal urine output.⁽⁴³⁾

In healthy adults, urine production is roughly 70 mL/h to 80 mL/h while awake and 30 mL/h to 40 mL/h while asleep. Similar to enuretic children, adults with PNE have an increased production of urine relative to the functional bladder capacity which plays an important role in the pathophysiology of enuresis. However, the underlying mechanism for this abnormal diurnal rhythm of urine production seems to be different in adults. With aging, the rate of nocturnal urine production increases while total daily urine production remains constant. In addition, concentrating ability of the kidney and activity of the renin-angiotensin axis both decrease.⁽⁴⁴⁾ It seems that the circadian rhythm of AVP declines with age, leading to similar hormone levels during day and night.⁽⁴⁵⁾

In 1998, Hunsballe and colleagues reported the results of a study comparing nocturnal urine output in 24 patients (mean age, 21.5 years; range, 15 to 37 years) who had MPNE with a control group of

9 healthy subjects.⁽⁴⁶⁾ Patients were subdivided into desmopressin responders and nonresponders. Urine outputs demonstrated an abolished circadian rhythm only in the desmopressin responding group with nocturnal polyuria and poorly concentrated urine at night. In contrast, desmopressin nonresponders had a significant variation in urine production similar to healthy controls with a decrease in urine output from day to night. Interestingly, AVP did not increase in either controls or desmopressin nonresponding enuretics at night, which further confirmed the result of previous studies pointing to the lack of diurnal variation in AVP in older healthy adults. On the other hand, no evidence of oscillation in AVP was encountered in desmopressin responders, either, and nocturnal AVP levels were again similar to healthy adults.

In another study, Hunsballe and coworkers compared urine volume and plasma AVP levels before and during a 24-hour water deprivation test in adults with PNE.⁽⁴⁷⁾ A significant decrease in urine output was noted after water deprivation in enuretic patients. Again, plasma AVP levels were normal in enuretic adolescents and adults regardless of response to desmopressin. Moreover, magnetic resonance imaging characteristics of the pituitary gland in 8 adults suffering from PNE have demonstrated no detectable pathology.⁽⁴⁸⁾ These findings led to the conclusion that unlike enuresis in children, nocturnal polyuria in adults has not been related to nocturnal hyposecretion of AVP, and nocturnal polyuria in adults may result from reduced renal tubular sensitivity to endogenous AVP or abnormal excretion of solutes.

In summary, the normal circadian rhythm of AVP production fades with age, and nocturnal polyuria, still an important factor in adult enuresis, seems to result from non-AVP-mediated mechanisms in this group of patients.

Sleep and Central Nervous System Function

Neither nocturnal polyuria nor diminished functional bladder capacity adequately explains why patients with NE do not wake up to void. A problem with arousal is therefore a prerequisite for enuresis to occur. Controversy has existed about the role of sleep disturbance in bringing about the enuretic

event. Over the past three decades, sleep investigation among nocturnal enuretic patients has evolved steadily.

It is still believed that enuretics are deep sleepers. Results of the large survey in Hong Kong showed significantly higher incidence of sleep disturbances in adults with PNE compared to healthy subjects.⁽¹³⁾ Difficulty in entering the sleep state and staying asleep, and early awakening were all more frequent in enuretic adults than in normal controls. In other studies, however, abnormality in the sleep pattern of enuretic patients has not been noted.⁽⁴⁹⁾ It has also been showed that bed-wetting can occur during all sleep stages.⁽⁴⁹⁾ These findings suggest that PNE may be associated with a problem of arousal from any stage of sleep rather than the depth of sleep.

Lack of success in finding any abnormalities of sleep pattern in some previous studies could be in part due to inaccurate measurement of sleep staging. Currently, a classic polysomnographic scoring technique according to the criteria defined by Rechtschaffen and Kales⁽⁵⁰⁾ is being used in sleep studies. In 2000, Hunsballe compared sleep patterns in 11 patients with PNE (mean age, 23.0 years; range, 15 to 49 year) with 10 healthy age-matched controls.⁽⁵¹⁾ Conventional polysomnography and a computerized electroencephalographic power analysis were used. An increased delta-wave energy was found among enuretic patients compared to healthy controls, reflecting abnormally deep sleep in adolescents and adults with MPNE. They concluded that “manual sleep scoring might inadequately reflect the sleep process.” Moreover, no sleep-modulating effect of desmopressin was found in this study. This finding was in contrast to the results of previous studies suggesting the sleep-modulating effect of AVP.^(52,53)

In summary, sleep factors are the common pathway in translating production/storage discord into enuresis, and difficulty in arousing from any stage of sleep is disputably influenced by AVP.

MANAGEMENT

Primary Care Awareness

“In most European countries, primary nocturnal enuresis is not necessarily considered as a disease

per se, particularly by the medical community; as a consequence, there is no specific education at medical school, and a poor involvement from the practitioners.^{(32)”} A study conducted among adolescents and young adults (mean age, 15.3 years; range, 13 to 23 years) has shown 20% of enuretic adolescents to have never consulted a doctor about their problem.⁽²⁰⁾ Among enuretic adolescents consulting a specialist, more than 40% received no therapy. Most consulted caregivers were pediatricians.

In the study of Yeung and associates, the percentage of adults with PNE who had never sought medical attention or therapy in Hong Kong was found to be 37% among 47 patients with PNE (mean age, 20 years; range, 16 to 43 years).⁽²⁹⁾ In addition, the incidence of depression and lowered self-esteem was significantly higher in enuretic adults. About one-third of the patients believed that this condition had negatively affected their job choice, work performance, and social activities; and 23% felt it had an impact on their family life and making friends for either sex. Similarly, results of the survey performed by Hirasing and colleagues showed that NE was associated with a great psychosocial impact.⁽¹²⁾ Of 57 patients with NE, one-third were concerned about bed-wetting and one-third were depressed. Due to bed-wetting, 33% of the patients were reluctant to go on holidays and 23% said it complicated their relationships. Despite such a negative impact on their life, 40% of the patients in this study had never consulted a care provider.

In summary, evidence attests to the great impact of adult enuresis on people’s lives, and at the same time, it points to the need for enhancing awareness about the problem and treatment options among the public and health care providers, alike.

Evaluation

A similar assessment as for children is justifiable as the initial step in evaluating adults with PNE. Initial assessment should focus on distinguishing between the possible definable and perhaps treatable causes of complex bed-wetting in enuretic adults. In such patients, the age of onset, length and circumstances of dry spells, number and timing of episodes of NE, sleep habits, and psychosocial situation should all be elicited. The patient should also be asked about any history of urinary tract infection, presence of daytime

voiding symptoms, and frequency and consistency of bowel movements. The physician should consider PNE as a diagnosis of exclusion, and all other causes of bed-wetting must be ruled out.

A list of urological causes for nonmonosymptomatic bed-wetting and clues to their diagnosis is provided in Table 3.

Physical examination in a patient suffering from NE might provide clues to a structural problem as the cause. It may reveal tell-tales of neurological abnormality. A thorough genital examination should be performed in all patients for possible anatomical abnormalities such as epispadias and ectopic ureter. The main utility of physical examination lies in guiding further workup by excluding or suggesting underlying bladder dysfunction.

In children, a carefully obtained history, physical examination, and a routine urinalysis are often sufficient for establishing the correct diagnosis and determine whether nocturnal polyuria or reduced functional bladder capacity are present. Further urodynamic investigation and imaging are indicated only for patients in whom day symptoms present or when conventional treatment fails.⁽³²⁾ However, in enuretic adults, whether having daytime symptoms or not, additional urodynamic evaluation seems necessary at an early stage. In urodynamic evaluation

of 30 patients with PNE, Yeung and colleagues found more than 90% of the patients to have detrusor overactivity, while only 38% had daytime urinary symptoms.⁽²⁹⁾ In addition, 6.7% of patients had a previously undiagnosed lesion causing some form of anatomical bladder outflow obstruction, 1 with congenital obstruction from posterior urethral membrane, and 1 with Moormann's ring. In the study performed by Wadie, 35% of patients with detrusor instability had neither diurnal urgency nor incontinence.⁽³⁰⁾ These urodynamic studies, together with the fact that PNE of adults represents a more pronounced and refractory form of enuresis, suggest that urodynamic evaluation and contrast imaging of voiding function should be performed as a part of the initial workup in all adults with PNE.

TREATMENT

The treatment approach to enuresis is controversial in large part due to the lack of consensus on the exact cause of enuresis, because so many factors either alone or together may contribute to this condition.

Generally, treatment can be divided into two broad categories: nonpharmacologic and pharmacologic. Nonpharmacologic treatment of enuresis includes motivational therapy, behavior modification (conditioning therapy), bladder-training exercises,

Table 3. Urologic Causes for Nonmonosymptomatic Bed-wetting*

Disorder	Clues for Diagnosis	Causes
Storage dysfunction		
Overactive bladder	Increased frequency, urgency, urge incontinence, history of wetting during the afternoon nap, history of wetting more than once per night	Idiopathic detrusor overactivity, neurogenic detrusor overactivity (eg, myelomeningocele, tethered cord syndrome, or spinal cord injury), urinary tract infection, polyuria (eg, diabetes mellitus, diabetes insipidus, or polyuric renal failure), DIDMOAD syndrome
Sphincter bypass	Continuous dribbling between voids	Ectopic ureter
Sphincter incompetence	Continuous dribbling between voids, stress incontinence, observed on physical examination	Urethral anomaly (epispadias or extrophy), spina bifida, sacralagenesis, iatrogenic(eg, post prostatectomy)
Voiding dysfunction		
Sphincter-active voiding	Overflow incontinence, voiding with a poor stream or strain, staccato voiding	Primary sphincter overactivity, previous urinary infection
Poorly contracting bladder	Overflow incontinence, voiding with a poor stream or strain, staccato voiding, infrequent voiding	Autonomic neuropathy (eg, diabetes mellitus, meningo-myelocele), lazy bladder
Urethral stricture	Overflow incontinence, voiding with a poor stream, or straining, observed on physical examination	Congenital (eg, posterior urethral valves, Cobb's collar), acquired (eg, postcircumcision, balanoposthitis, traumatic)
Elimination dysfunction	Constipation, encopresis	Spinal cord abnormality

*DIDMOAD indicates diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.

psychotherapy, diet therapy, and hypnotherapy.

Based on the fact that NE may result from nocturnal polyuria, small functional bladder capacity, and decreased arousal response to the full bladder, pharmacologic treatment modalities can be defined under 3 subsets. To regulate the sleep-awake center in the brain, amphetamine, imipramine, and diazepam are used. Calcium channel blockers, prostaglandin inhibitors, and α -adrenoreceptor inhibitors are utilized for pathological conditions of bladder-sphincter complex, and desmopressin is meant to induce antidiuretic effect at the kidney level. Recent studies have shown that many of these drugs have different mechanisms of action, and division into these subgroups may therefore be inaccurate.

These drugs have been used with varying degrees of success, and many studies provide supporting evidence for each approach. However, much of these data comes from enuretic children, and evidence for or against the use of different treatment modalities in the enuretic adult is limited.

Alarm Therapy

Alarm therapy is currently recommended as the first choice for children suffering from NE.⁽³²⁾ There is a good deal of evidence to support alarm therapy as the most effective treatment with reproducible rate and durable results in enuretic children, achieving dryness in more than 50% of patients.^(54,55) Moreover, on the long run, alarm therapy would appear to be the most clinically effective and cost-effective intervention.^(56,57)

Unfortunately, treatment with bed-wetting alarms has a dropout rate of 10% to 30%.⁽⁵⁸⁾ To achieve optimal results, alarm therapy requires a motivated patient and family and significant commitment of effort and time.⁽³²⁾ These considerations make alarm therapy a less favorable choice in enuretic adolescents and adults. Studies have shown that most enuretic adults prefer not to use alarm therapy or discontinue it very soon. In a large survey involving 11 406 noninstitutionalized adults (age range, 18 to 64 years), the number of patients who had ever tried the alarm was very low (about 7%) among 57 adults with NE.⁽¹²⁾ Similarly, Nappo and colleagues reported on characteristics of enuretic adults in Italy⁽²⁰⁾; of 107 patients suffering from NE, only 8 had tried alarm therapy after desmopressin failure. Two

discontinued therapy and stopped it very soon, one due to discomfort and not awakening and the other (an obese patient) due to frequent false alarm caused by perspiration.

The main reason for low compliance with alarm therapy in adolescents and young adults seems to be the time it is required for alarm therapy to take effect. Many patients request for a treatment modality with a rapid action. In addition, they believe that alarm therapy would disrupt others' sleep and/or make their private problem public. It has been shown that adults who use the alarm (even those who are cured) recall the treatment period as the worst time of their life.^(34,59)

Despite the high dropout rate in adults, evidence still suggests that alarm therapy enjoys a comparable success rate in compliant patients. An uncontrolled trial of patients with MPNE was conducted by Vandersteen and Husmann to determine the efficacy of alarm therapy versus medical therapy.⁽⁶⁰⁾ In this study, 29 patients (median age, 20 years; range, 18 to 33 years) were treated with desmopressin, alarm therapy, and imipramine, consecutively. Patients who remained incontinent with the maximum dose of desmopressin or whose NE returned after weaning desmopressin were treated with an enuretic alarm system. Two-thirds of the patients were continent on desmopressin for 6 months, of those only 7% remained continent when weaned from the medication.

On the other hand, in another study, alarm therapy had much lower initial success rate (33%), but this response was durable and all patients remained continent at 18 months' follow-up. Although the patients were informed about the importance of perseverance, 56% had discontinued therapy within 6 weeks. The investigators attributed the low success rate to noncompliance. In the complier group, success was 75%, very similar to the 79% rate observed in the compliant children.⁽⁶¹⁾ It was concluded that children and adults respond equally well to alarm therapy if they adhere to the treatment protocol.

The effect of alarm therapy can be enhanced by adding behavioral components such as arousal training, overlearning, full spectrum home treatment, and dry-bed training (DBT).

Dry-bed training refers to regimens that include enuresis alarm, waking routines, positive practice, cleanliness training, bladder training, and rewarding, in various combinations. Developed by Azrin and associates,^(62,63) it is probably the most successful therapy for children of different ages and is usually tried as the last resort for resistant patients after failing on simple alarm and pharmacotherapy.⁽⁶⁴⁾

In 2 studies by von Son and colleagues on 9 patients treated with DBT, continence (dry during for consecutive weeks) was achieved between 4 and 21 weeks after the first treatment. Relapse occurred in 3 patients after complete response and in 4 during the 6-year follow-up. Of the patents with recurrence, 1 received a booster training to achieve continence and 1 became continent after using desmopressin.^(65,66) The success and relapse rates were not significantly different between primary and secondary enuretics. No relapse during DBT was the only predictor of further relapses. Age, gender, type of NE (primary versus secondary), and reported lighted or deep sleep were not identified as predictors of relapse.

In summary, conditioning by the alarm and behavioral modification suffer from great dropout due to being effort intensive and time consuming. Nevertheless, these methods retain their high efficacy and durability in enuretic adults, too.

Desmopressin

Desmopressin, a synthetic analogue of AVP, results in increased reabsorption of water by the kidney, forwarding a smaller volume of more concentrated urine to the bladder and reducing 2-hour urine production.⁽⁶⁷⁾ Desmopressin is 2000 to 3000 times more potent than AVP and its duration of effect is also 5 times longer.⁽⁶⁸⁾ The antidiuretic effect of desmopressin is mediated through the V2 receptor acting on collecting ducts of the kidney.⁽⁶⁹⁾ By a yet unknown mechanism, desmopressin triggers the redistribution of water channel (aquaporin-2) into the apical membrane.⁽⁷⁰⁾ It has been suggested that its beneficial effect on enuresis is not entirely due to its antidiuretic activity, but this needs further proof.

In a human study performed by Born and colleagues, intravenous infusion of AVP caused significant decrease in rapid eye movements at sleep and subjects woke up easier.⁽⁵²⁾ The authors concluded

that enuretic patients may benefit from this effect of desmopressin on the sleep-awake center. In addition, it has been shown that desmopressin might interact with the serotonergic system.^(71,72)

Desmopressin has been utilized in adults in both forms of nasal spray (20 µg/spray) and oral tablet (0.2 mg). The usual dose is 20 µg to 40 µg, intranasal, or 0.2 mg to 0.4 mg, oral, at bedtime regardless of age or weight.⁽⁶⁷⁾ It has no vasopressor or smooth muscle activity in the therapeutic dose range, and its effect lasts for 7 to 12 hours.⁽⁶⁹⁾ Desmopressin is the first-line pharmacotherapy agent for NE in children,⁽⁷³⁾ with a partial (50% to 90% reduction in wet night) and full (at least 90% reduction) response rate ranging from 10% to 90%.^(74,75) It produces a more rapid improvement than alarm therapy (reduction of urine output on the first night of therapy). However, these benefits are temporary, with a high relapse rate ranging from 50% to 100% once the treatment is discontinued.^(76,77)

Trials in adults with PNE have yielded comparable outcomes with studies in children. In a randomized, double-blind, cross-over trial of 25 patients resistant to alarm therapy (age range, 11 to 21 years) on desmopressin 200 µg/day to 400 µg/day for 24 weeks, Stenberg and Lackgren found that a titrated dose of oral desmopressin in comparison with placebo was associated with a reduction in the number of wet nights per week.⁽⁷⁸⁾ In addition, 400-µg tablets were found to be more effective than 200-µg ones in NE.

The reported efficacy of this drug in the treatment of NE persisting into adulthood varies partly, because the study population is not always homogenous, and the prevalence of voiding disorders is not always reported. Monosymptomatic PNE is a different clinical entity from enuresis associated with diurnal voiding disturbance, and the study population should therefore be distinct to correctly evaluate drug efficacy. In 1996, Janknegt and coworkers reported the results of a randomized multicenter trial in 66 patients with PMNE (mean age, 19.4 years; range, 12 to 45 years) who received either desmopressin, 200 µg or 400 µg, for 4 weeks followed by 12 weeks of open-labeled treatment with desmopressin, 400 µg.⁽⁷⁹⁾ Fifty-seven percent of the patients responded completely to desmopressin. The difference between the 4 weeks' treatments with 200 µg and 400 µg

of desmopressin was not significant. However, patients who initially received 200 µg experienced an additional decrease in the number of wet nights after receiving 400 µg of desmopressin. Similarly, Vandersteen and Husmann, treating 29 patients with PNE (median age, 20 years; range 18 to 33 years), reported a 66% full response rate (no or one wet night per month) under desmopressin therapy.⁽⁶⁰⁾ However, the benefit of desmopressin was temporary with 93% relapse from 3 days to 6 weeks after discontinuation of desmopressin.

Nocturnal polyuria and a low nocturnal urine osmolality are characteristic of children with enuresis that respond favorably to the treatment with desmopressin.⁽⁴⁶⁾ Similarly, the response to desmopressin in enuretic adults has been shown to be related to nocturnal polyuria. In 1998, Hunsballe and colleagues evaluated the treatment response to desmopressin in 24 patients (age range, 15 to 37 years) with MPNE and compared them with 9 healthy subjects (age range, 24 to 31 years).⁽⁴⁶⁾ The results demonstrated a significantly high pretreatment nocturnal urine volume in desmopressin responders in comparison with nonresponders and controls. The urine osmolality was also significantly lower in desmopressin responders. Daytime values of urine output and urine osmolality did not differ significantly among the groups. In children, a better response to desmopressin has been found in patients with larger bladder capacities.⁽⁸⁰⁾ A study of 20 PNE adult patients (mean age, 27.1 years; range, 20 to 42 years) revealed that response to desmopressin was not related to the urodynamic profile. Of 10 patients responding to desmopressin, 6 (60%) had normal urodynamic profiles and 4 (40%) had detrusor instability and/ or hypocompliance.⁽³¹⁾ In addition, the relapse rate was also not related to the urodynamic profile.

A study of 107 PNE adults demonstrated no association between response to desmopressin and age, gender, family history, or severity of NE in adults.⁽²⁰⁾ Some controversy exists as to whether a family history of NE is a positive predictor for good response to desmopressin or not.⁽⁸¹⁾

The results of numerous clinical trials have shown desmopressin to be generally well tolerated even during long-term treatment (1 year or more) and associated with a low incidence of adverse events.⁽³²⁾

Side effects appear to be dose related, and temporary cessation of the drug commonly leads to their resolution.^(82,83) In a study involving 7 patients with PNE (mean age, 17.7 years; range, 10 to 26 years) long-term desmopressin therapy (mean duration, 13 months; range, 4 to 24 months) was not associated with any abnormalities in hematological, biochemical, and hormonal parameters examined in the study.⁽⁸⁴⁾

Adverse effects of desmopressin include headache, tinnitus, sore throat, dizziness, nausea, abdominal pain, elevated blood pressure, and local irritation by using intranasal administration such as rhinorrhea, nasal congestion, epistaxis, and ulceration. The major but rare adverse effect of desmopressin is water intoxication with severe hyponatremia which occurs mostly in children. Only 5 cases have been reported in adults with PNE under therapy with desmopressin.⁽⁸⁵⁾ Their desmopressin dose ranged from 20 µg to 80 µg, daily, and serum levels of sodium ranged from 114 mmol/L to 124 mmol/L. Seizures developed in most patients.

The common history leading to this serious side effect is a considerable intake of water while taking desmopressin.⁽⁸⁵⁾ To minimize this risk, it has been recommended that daily fluid intake should be limited to 1 liter in a healthy 70-kg adult taking desmopressin.⁽⁸⁶⁾ It is suggested that the intake of all fluids be restricted to the minimum tolerable amount within the 12 hours following administration, because the effect of desmopressin usually lasts 6 to 12 hours. Serum sodium levels should be measured in patients taking the drug 24 to 48 hours, 1 week, and 1 month after beginning treatment. In addition, it should be used cautiously in disease states in which rapid increase in extracellular fluid may impose risks (eg, in angina, hypertension, and heart failure). The drug is likewise prohibited in patients with acute renal failure.⁽⁶⁹⁾

In summary, desmopressin remains the most rapidly acting tool for symptomatic control of adult enuresis and has a reasonable safety profile in this group; however, it is notorious for posttreatment recurrence.

Lastly, those patients in whom urodynamic study and imaging suggest significant bladder dysfunction deserve specific medical treatment tailored to their specific type of aberration (including antimuscarinics, smooth muscle relaxants, botulinum toxoid, and

clean intermittent catheterization as required). Nonresponders would naturally be considered for augmentation cystoplasty. Discussion of these subjects is beyond the scope of this article.

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